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Commentary and concepts

San Antonio Vasopressin in Shock Symposium Report☆,☆☆

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ABSTRACT

The San Antonio Vasopressin Symposium reviewed substantial accumulated data concerning vasopressin in haemorrhagic, septic, and cardiac arrest shock conditions and found that there is considerable evidence to support the use of vasopressin in overcoming vasopressin deficiency or insufficiency. The value of vasopressin in the setting of trauma requires further investigation. It was concluded that a large, multicenter controlled trial of vasopressin is needed to assess the therapeutic benefit of vasopressin replacement in the setting of trauma with haemorrhagic shock that is prolonged and profound.

1. Introduction

From the Persian Gulf War (1990–1991) to the present conflict in Iraq and Afghanistan, the mortality of U.S. injured soldiers decreased from 24% to 10%, most likely due to improvements in trauma care which include: far forward surgery; protective equipment; rapid evacuation; and adoption of tactical combat casualty management protocols.[1,2] Despite these advances, haemorrhagic shock continues to be the major cause of death in combat and civilian settings, and there remains little scientific evidence supporting the current management of individuals who have sustained injury resulting in uncontrolled haemorrhagic shock.[3] On September 3, 2009, a Symposium sponsored by the University of Texas Health Sciences Center, Department of Surgery, and the U.S. Army Institute of Surgical Research was held in San Antonio, Texas, which focused upon the potential benefits of vasopressin use in shock.

2. Vasopressin deficiency states and shock

While a vasopressin infusion has little vasopressor effect in normal subjects due to a baroceptor-mediated decrease in heart rate, vasopressin infusions are being used successfully in catecholamine-refractory vasodilatory shock.[4] Vasopressin levels from 0 to 5–7 pg/ml fully regulate urinary concentration. But, in vasodilatory shock, levels <10 pg/ml constitute an absolute deficiency and 10–30 pg/ml a relative deficiency.[5] Vasopressin replacement at 0.04 U/min results in a plasma concentration of approximately 100 pg/ml and restores arterial blood pressure by a direct vasopressor effect and by increasing sensitivity to pressor catecholamines. At low doses (1–2 IU/h) in the setting of vasodilatory shock, vasopressin does not compromise the cerebral, splanchnic or coronary circulations.[4]

Vasopressin deficiency and hypersensitivity has been demonstrated in vasodilatory septic shock, post cardiopulmonary bypass, in milrinone induced vasodilatory shock, in shock post brain death and in irreversible shock.[4] Irreversible shock is a late vasodilatory phase of any type of shock that develops if the shock state is suf-

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ficiently profound and prolonged. The late phase of haemorrhagic shock is also a vasodilatory state characterized by vasopressin deficiency and pressor hypersensitivity in rat and dog cohorts, and in isolated human subjects. The precise definition of vasopressin insufficiency or deficiency during various stress states remains uncertain.[6]

3. Vasopressin in septic shock

The VASST (Vasopressin And Septic Shock Trial) study provides some important insights into the effects of vasopressin infusion and also provides some useful lessons that may be relevant in a clinical trial of vasopressin in traumatic haemorrhagic shock. The overall result showed no statistically significant difference in 28-day mortality between the addition of low dose vasopressin (35% mortality) versus noradrenaline (norepinephrine) (39% mortality) in patients who had severe septic shock (all were pressor dependent at study entry).[7] It should be noted that low dose vasopressin lowered mortality in a prospectively defined subgroup of less severe septic shock (about half the patients), from 36% to 27% ($p = 0.05$). Conversely, mortality in patients with extreme severity of illness was unresponsive to treatments.

Additional important information arose that may be useful in future vasopressin trials. First, and most importantly, there were no differences in serious adverse events between the vasopressin and noradrenaline treated groups. Second, the low dose of vasopressin used in VASST, 0.03 IU/min, resulted in an increase in plasma vasopressin levels from ~2 pg/ml at baseline to 80–120 pg/ml. Of note, specific genetic polymorphisms may appear to predict which patients benefit from vasopressin treatment, and which patients may have an adverse response.[8]

4. Vasopressin in brain injury

Traumatic brain injury is among the leading causes of trauma death and disability in both civilian and military populations. To minimize cerebral ischaemic episodes, most treatment protocols are aimed at optimising cerebral perfusion pressure. The cornerstones of these treatments include mannitol, to reduce intracranial pressure, and catecholamines, such as phenylephrine, to increase mean arterial blood pressure, but these agents have undesired side effects. In clinically relevant laboratory models, vasopressin has been demonstrated to be safe and effective during initial fluid resuscitation, rapidly restoring haemodynamics, reducing fluid shifts and improving survival.[9,10] Recently, a clinical trial was initiated, NCT00795366 (www.clinicaltrial.gov), to develop a new therapeutic option for cerebral perfusion pressure management in traumatic brain injury patients using vasopressin. The trial aims at defining risks and benefits of vasopressin therapy relative to routine vasopressor use, and evaluating this new therapy relative to the current evidence-based guidelines for cerebral perfusion pressure management in the brain injured.

5. Vasopressin in cardiac arrest

Data was reported which suggested a potential benefit of vasopressin compared to adrenaline (epinephrine) (the standard of care) in the resuscitation of out-of-hospital cardiopulmonary arrest. Laboratory studies previously confirmed that exogenous vasopressin given during cardiac resuscitation improved vital organ blood flow. While two large out-of-hospital cardiopulmonary resuscitation trials failed to extrapolate advantages of vasopressin from the laboratory to emergency cardiac care in the streets, it is possible that outcome was impaired by the degree of underlying fundamental ischaemia thus overshadowing the effects of advanced cardiac life support.[11–13] In contrast, vasopressin appears to have beneficial effects in studies with moderate ischaemia, especially in combination with catecholamines.

6. Vasopressin in haemorrhagic shock

It has been hypothesized that vasopressin may be beneficial to stabilize blood pressure in posttraumatic haemorrhagic shock when standard shock therapy fails, especially when uncontrolled haemorrhagic shock is present.[14] Observations have been previously made in the setting of uncontrolled haemorrhagic shock (both bleeding laboratory animals and trauma patients), that vasopressin shifts blood away from the musculature, skin and gut towards the heart and brain.[15] Vasopressin has manifested a clear superiority over fluids and, or catecholamines in a porcine liver haemorrhage models.[16] However, there is little clinical data on the efficacy of exogenous vasopressin in the setting of haemorrhagic shock following trauma.[17]

A European multicenter trial to determine the role of vasopressin in prehospital trauma is currently being initiated in Austria and Germany.[18] Patients who do not sufficiently respond to standard therapy with aggressive fluid resuscitation, tracheal intubation, mechanical ventilation and catecholamine vasopressors will receive vasopressin (www.vitris.at). Unfortunately, as the funding situation for academic trials in Europe is very difficult, this trial has to be deemed exploratory due to the small number of anticipated patients ($n = 200$). Thus, a larger study is needed in order to determine the clinical value of vasopressin in severe haemorrhagic shock.

Others have found that, irrespective of the type of animal injury model, resuscitation strategies that minimize the total fluid administered lead to improved outcomes. Subsequently, a double-blind randomized study, NCT00420407 (www.clinicaltrials.gov) was performed to assess the safety and efficacy of vasopressin as an additive to resuscitative fluid. Following a bolus [placebo or 4 IU vasopressin], intravenous infusion was given at 200 ml/h for 5 h, [vasopressin group received 2.4 IU/h and the control group received placebo]. Patients included met all of the following criteria: ≥18 years of age; systolic blood pressure ≤90 mmHg; clinical evidence of acute traumatic injury; and infusion of study drug started ≤1 h after a systolic blood pressure ≤90 mmHg. Unfortunately, this study was terminated early due to difficulties with patient recruitment; 78 patients were randomized under exception from informed consent for emergency research [FDA 21 CFR 50.24]. The groups were well matched for age, gender, pre-existing medical illnesses, and weight. Injury mechanism and severity of injury (about 29) were also similar. Serum vasopressin levels, measured in a random subset of patients was in the range of moderate vasopressin insufficiency upon admission; post infusion, vasopressin levels were maintained in the vasopressin group, but decreased statistically significantly into the vasopressin deficiency range in the control group; and remained at these same levels in both groups over 12 h. Total fluids over the first 5 days across all time points were statistically significantly less in the vasopressin group. Twenty-four hour and 5-day mortality was substantially reduced in the vasopressin group (by about 50%), but these changes did not reach statistical significance (unpublished data). This study suggests a possible early survival advantage with the use of vasopressin after severe trauma.

7. Summary

The San Antonio Vasopressin Symposium reviewed substantial accumulated data concerning vasopressin in haemorrhagic, septic, and cardiac arrest shock conditions and found that there is consid-

erable evidence to support the use of vasopressin in overcoming vasopressin deficiency or insufficiency. The value of vasopressin in the setting of trauma requires further investigation. It was concluded that a large, multicenter controlled trial of vasopressin is needed to assess the therapeutic benefit of vasopressin replacement in the setting of trauma with haemorrhagic shock that is prolonged and profound.

Attendees

U.S. Department of Defense: L. Blackbourne[1] (Co-Chair), D. Hack[1], M. Given[3], B. Eastridge[1], C. Wade[1], D. Baer[1], J. Sondeen[1], C. Uyehara[4], D. Zonies[5], S. Savage[5], *Civilian*: S. Cohn (Chair) [2], D. Landry[6], V. Wenzel[7], K. Walley[8], D. Traber[9], K. Proctor[10], J. Michalek[2], B. Pruitt[2], B. Pollock[2], J. Langlois[11], and D. Soffer[12]. From the U.S. Army Institute of Surgical Research,[1] San Antonio, TX; University of Texas Health Science Center,[2] San Antonio, TX; Office of Naval Research,[3] Arlington, VA; Tripler Army Medical Center,[4] Honolulu, HI; Lackland Air Force Base,[5] San Antonio, TX; Columbia University,[6] New York, NY; Innsbruck Medical University,[7] Innsbruck, Austria; University of British Columbia,[8] Vancouver, B.C.; University of Texas Medical Branch,[9] Galveston, TX; University of Miami Miller School of Medicine,[10] Miami, FL; U.S. Department of Veterans Affairs,[11] Washington, D.C.; Tel Aviv Sourasky Medical Center,[12] Tel Aviv, Israel.

Conflict of interest statement

No author has a conflict of interest that relates to the content discussed in this manuscript.

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